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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,362	06/22/2001	Patrick J. Muraca	5568/1012	8909

29932 7590 01/13/2003  
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[REDACTED] EXAMINER

SRIEGLER, ALEXANDER H\*

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1637

DATE MAILED: 01/13/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	09/888,362	MURACA, PATRICK J.
	<b>Examiner</b>	<b>Art Unit</b>
	Alexander H. Spiegler	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 08 October 2002.

2a) This action is FINAL.                    2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-69 is/are pending in the application.

4a) Of the above claim(s) 16-34 and 66-69 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-15 and 35-65 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ .
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .	6) <input type="checkbox"/> Other: _____ .

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**DETAILED ACTION**

1. This action is in response to Paper No. 7, filed on October 8<sup>th</sup>, 2002. Currently, claims 1-69 are pending. In Paper No. 8, Applicants elected Group I (Claims 1-53) with traverse. However, after further consideration a new restriction requirement has been made.

*Election/Restrictions*

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-15 and 35-65, drawn to methods for preparing a microarray, the microarray made and methods for identifying the specificity of a molecular probe using said microarray, class 435, subclasses 5 and 6, for example.
- II. Claims 16-34, drawn to a microarray block comprising a plurality of donor tissue and/or cell samples, class 435, subclass 1.3, for example.
- IV. Claims 66-69, drawn to methods for identifying a candidate diagnostic probe, classified in class 435, subclass 6, for example.

3. The inventions are distinct, each from the other because of the following reasons:

A) Inventions (I and III) and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the microarray of Group II is not used in the methods of Groups I or III. Additionally, the microarray of Group II is not made by the methods of Group I, as evidenced by claims 35-53, which are the micrroarrays made by the methods of Group I. Thus, Group I and II are different chemical entities having differing biochemical structures, modes of operation, functions, and effects.

B) Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the process for using the product as claimed can be practiced with another materially different product, such as a microtiter plate, for example.

4. Because these inventions are distinct for the reasons given above and have acquired a different status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-III require different searches that are not co-extensive, examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Paula Campbell Evans on January 2, 2003 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-15 and 35-65. Affirmation of this election must be made by applicant in responding to this Office action. Claims 16-34 and 66-69 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

6. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

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application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 1-15 and 35-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Leighton (USPN 6,103,518), in view of Irving et al. (J of Clin. Path. (1996) 49: 258-259).

Leighton teaches a method for constructing tissue microarrays (also referred to as "tissue Chips") comprising,

"taking samples from a series of donor tissues, one at a time, using a hollow, preferably needlelike, donor punch and placing each sample sequentially in a recipient of complementary shape in a recipient material by a recipient punch, thereby forming an array of tissues in the recipient block. Each punch comprises a punch tube and an associated stylet guided within the diameter approximating that of the donor punch inner diameter, and is dimensioned for sliding within the punch tube. The process of forming a hole in a recipient material such as paraffin, taking a sample of tissue from a donor specimen, and planting this sample in the hole in the recipient material, is repeated until a tissue array is formed comprising hundreds of tissue samples arranged in assigned locations in the recipient material. (col. 7).

"Once the desired number of tissue samples have been transplanted from the donor block(s) to the recipient block, the "tissue chips" can be formed by slicing the tissue array block into hundreds of consecutive thin sections of, e.g., 5 micrometers in thickness, by traditional means (i.e., microtomes such as Model Cut .sub. 4055.TM. by Olympus Corp. of Tokyo, Japan, etc.; see, e.g., U.S. Pat. Nos. 664,118; 2,292,973; 2,680,992; 3,420,130; 3,440,913; 3,496,819; 3,799,029; and 3,975,977) to create multiple nearly identical sections, with each of the donor cores then being represented as minuscule dots on an ordinary glass microscope slide. Analyses that may be performed on the donor specimens include immunological analysis, nucleic acid hybridization, and clinicopathological characterization of the specimen." (col. 13).

Leighton also teaches:

"The sample punched from the donor tissue sample is preferably cylindrical, about 1-8 mm in length, with a diameter of from about 0.4 to 4.0 mm, preferably about 0.3-2.0 mm. The recipient punch is slightly smaller than the donor punch and is used to create a hole in a recipient block, typically made of paraffin or other embedding medium." (col. 7).

Leighton also teaches that the methods can be automated and information for each donor sample in the recipient block is stored in a database (col. 7). Leighton also teaches that this array can be used for many types of samples, including diseased samples (col. 1-4). It is also noted, that with respect to claims 54-65 (claims drawn to contacting the microarray with a molecular probe), Leighton teaches that the array made in his methods can be used in nucleic acid hybridization, which would inherent use a molecular probe for detection (e.g., determining which sublocation react).

Leighton teaches that the tissue samples are embedded in a block of paraffin or other embedding material. Leighton does not specifically teach the use of frozen embedding material.

However, Irving teaches that storing pathological tissue or cell specimens in OCT embedding material (i.e., a frozen embedding material) "permits retrospective analysis of RNA from small amounts of stored pathological samples" (see abstract). In other words, Irving teaches that embedding samples in OCT embedding material produces high quality RNA (i.e., RNA is not likely to get degraded in OCT, as it would in paraffin embedding material) (pg. 258).

In view of the teachings of Irving, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Leighton so as to have embedded tissue and/or cell samples in OCT embedding material, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when

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analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis).

10. Claims 1-15 and 35-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Leighton (USPN 6,103,518), in view of Goldsworthy et al. (Mol. Carcinog (1999) 25(2): 86-91).

The teachings of Leighton are presented above. Specifically, Leighton teaches the preparation of a tissue microarray, wherein the tissue samples are embedded in a block of paraffin or other embedding material. Leighton does not specifically teach the use of frozen embedding material.

However, Goldsworthy teaches that “frozen tissues yielded more RT-PCR product than did paraffin-embedded tissues” when analyzing liver tissue expression (see abstract and pg. 87). Goldsworthy concludes that one of the reasons for this is that, “the longer exposure of the fresh tissues to the fixative before embedding in paraffin may have resulted in RNA degradation from endogenous RNases, resulting in lower amounts of amplifiable RNA” (pg. 90, second column). Goldsworthy’s results, like others in the art, further support the idea that better results of amplification of RNA from tissues are obtained by using methods other than paraffin blocks (pg. 90, second column).

In view of the teachings of Goldsworthy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Leighton so as to have embedded tissue and/or cell samples in a frozen embedding material, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis).

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11. Claims 1-15 and 35-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (Pub. No. US 2002/0132246), in view of Irving et al. (J of Clin. Path. (1996) 49: 258-259).

Kallioniemi teaches a method for making a tissue microarray:

"In a specific example, core tissue biopsies having a diameter of 0.6 mm and a height of 3-4 mm, were taken from selected representative regions of individual "donor" paraffin-embedded tumor blocks and precisely arrayed into a new "recipient" paraffin block (20 mm.times.45 mm). H&E-stained sections were positioned above the donor blocks and used to guide sampling from morphologically representative sites in the tumors. Although the diameter of the biopsy punch can be varied, 0.6 mm cylinders have been found to be suitable because they are large enough to evaluate histological patterns in each element of the tumor array, yet are sufficiently small to cause only minimal damage to the original donor tissue blocks, and to isolate reasonably homogenous tissue blocks.

With the adhesive film in place, a 4-8 .mu.m section of the recipient block is cut transverse to the longitudinal axis of the tissue cylinders (FIG. 5) to produce a thin microarray section 76 (containing tissue specimen cylinder sections in the form of disks) that is transferred to a conventional specimen slide 78. The microarray section 76 is adhered to slide 78, for example by adhesive on the slide. The film 74 is then peeled away from the underlying microarray member 76 to expose it for processing. A darkened edge 80 of slide 78 is suitable for labeling or handling the slide." (pg. 5, Figs. 1-10 and 15-17).

Kallioniemi teaches that the samples can be that the methods can be automated and information for each donor sample in the recipient block is stored in a database (pg. 5, for example). Additionally, Kallioniemi teaches microarray can be used for many types of samples, including diseased samples (pgs. 1-4, Ex. 1-14). Kallioniemi also teaches methods including contacting the microarray with a molecular probe (pgs. 1-4, for example).

Kallioniemi does not specifically teach the use of frozen embedding material.

However, Irving teaches that storing pathological tissue or cell specimens in OCT embedding material (i.e., a frozen embedding material) "permits retrospective analysis of RNA from small amounts of stored pathological samples" (see abstract). In other words, Irving

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teaches that embedding samples in OCT embedding material produces high quality RNA (i.e., RNA is not likely to get degraded in OCT, as it would in paraffin embedding material) (pg. 258).

In view of the teachings of Irving, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kallioniemi so as to have embedded tissue and/or cell samples in OCT embedding material, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis).

12. Claims 1-15 and 35-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (Pub. No. US 2002/0132246), in view of Goldsworthy et al. (Mol. Carcinog (1999) 25(2): 86-91).

The teachings of Kallioniemi are presented above. Specifically, Kallioniemi teaches the preparation of a tissue microarray, wherein the tissue samples are embedded in a block of paraffin. Kallioniemi does not specifically teach the use of frozen embedding material.

However, Goldsworthy teaches that “frozen tissues yielded more RT-PCR product than did paraffin-embedded tissues” when analyzing liver tissue expression (see abstract and pg. 87). Goldsworthy concludes that one of the reasons for this that, “the longer exposure of the fresh tissues to the fixative before embedding in paraffin may have resulted in RNA degradation from endogenous RNases, resulting in lower amounts of amplifiable RNA” (pg. 90, second column). Goldsworthy results, like others in the art, further support the idea that better results of amplification of RNA from tissues are obtained by using methods other than paraffin blocks (pg. 90, second column).

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In view of the teachings of Goldsworthy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kallioniemi so as to have embedded tissue and/or cell samples in a frozen embedding material, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis).

***Conclusion***

13. No claims are allowable.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler  
January 9, 2003

*Kenneth R. Horlick*  
KENNETH R. HORLICK, PH.D  
PRIMARY EXAMINER

1/9/03